The next thing we're going
to do is look at how you go about
targeting pathogens. That is not just the
adaptive with antibodies, but also a variety of innate
techniques to basically even precure you from
various kinds of infections. Here is a reminder, and you have this chart in your outline so heaven for fend, you should try and go and
rewrite the whole thing again. But we're just going to look at some examples of various
pathogens and how you might be able to tell they're bad guys even before you have a chance to make
antibodies against them. First of all, here's a reminder. This is actually a flu virus
that's been popped open, and you can see some of the single stranded
RNAs in the middle. One thing that you get from
a flu or any other kind of virus is that they're
usually recognized by something funky in that
internal nucleic acid, because it turns out that
the outer parts here, the plasma membrane
and the proteins, the plasma membrane has
been borrowed from a cell, the proteins are again made, but they're not made to a
pattern that you can recognize. Viruses are usually
recognized by something unusual in
their nucleic acids. We get into bacteria. Bacteria will give
you all kinds of wonderful opportunities to
tell that they're not you. In particular, they're flagella. Their DNA has methylation patterns that are different from yours. They have cell wall compounds. They have lipid sticking out. They have a whole variety of different compounds that are strictly prokaryotic compounds, and you can tell they're not you because you're a eukaryote. Here is some yeast. This is candida as
a matter of fact. I'm not quite sure if
you can see in this, but this is also as
we are a eukaryote, but it's quite
different from us. In particular, it has
cell wall compounds, something we'll
return to again that your innate immune system, can recognize right away as being something that
shouldn't be there. Now, your innate immune
system has a bit of a tougher time with things
like unicellular eukaryotes. This is giardia, something
that can cause diarrhea. It looks like it has these cute little eyes looking at you, but those are not eyes. Those are actually two
adhesion plates that they use to stick to the
side of your intestine. You can see it has flagella, but these are
eukaryotic flagella, basically similar to
the kind you have. There are not a whole lot of pattern molecules that
are unique to eukaryotes. There are some things
in their surfaces. We can see that also
here with this one, this is a tripanosome, that's again, a nucleus and
not an eye looking at you. They have, again, the
eukaryotic flagella. These guys are a little
bit tougher to recognize. Here is a very
interesting tapeworm stuck in somebody's intestine. We can see that tapeworms are going to also have a few things in their outer surface you can recognize, but these guys are also
going to be a little bit harder to distinguish from
you because like you, you and I and tapeworms, are all multicellular
eukaryotic animals and so you've got to find
something a little bit different to find the
wedge between the way they have their physiology and run their lives
and the way you do. That's going to be a
little bit tougher. This is the first thing that
we're going to look at, and this is actually

a mock up or a diagram of what we think a bacterial
flagellum looks like. When we're looking to find ways of getting rid of
pathogens, we're looking for patterns in
the pathogens that we can. Ordinarily, we don't recognize proteins with
pattern recognition receptors, but this protein we do. Anything that we're
going to recognize with a pattern recognition receptor
will be something that you can't change very significantly without changing the
function and making it non-functional. If we're looking
at a protein, say, in a viral coat, flu can
mutate that a little bit. It'll still work, and your
antibodies can't recognize it. But the recognition by a pattern recognition
molecule is going to be a bit more
general and if I change these components to this
flagellum molecule, I would have a flagellum
that didn't work at all. As it turns out, there are very few proteins that
we recognize innately. Flagellin is one,
and another one interestingly enough is
something called profilin. Now, this is it turns out
to be the same molecule that you actually use to help organize your
microfilaments. But there are parasites that produce a large amount of
it and actually use it to slide around on
so lots and lots of profilin on the outside of
a cell is a very bad thing. Now, what we are really good
at recognizing, however, is a variety of carbohydrates and their associated
molecules. Here is another fungal cell. Fungi have in them a cell wall
component called zymosan. That's a little bit
of a vague term. It turns out to be
a Beta-1,3-glycan, that is glucoses stuck together
by one and three carbons. Fungi also have chitin which
has the sugar same glucose, stuck together 1,4, just like cellulose,
except each glucose has an acetylglucosamine on it, and an amine group
on the glucose. You would think that that
would be a good thing for pattern
recognition molecules, but they seem to go for the
Beta-1,3-glycan instead. Now, there are also something
we call peptidoglycans. This is what we have a lot of
in gram-positive bacteria. Here is the cross section
through the plasma membrane and a thick cell wall of a
gram-positive bacterium. They can actually
have up to 40 layers of this complex wall material. You can see they also have
some lipids sticking out. What we're going to do
is take another look at that peptidoglycan. Here is another thing that shows you
how it's put together. You have glucose or
various kinds of carbohydrate units,
and acetylglucosamine, neuraminidase, and
they're cross-linked in a screen like structure
with tetrapeptide. You have the peptides going in one direction and the
glucose going in another. It turns out you can
actually make this into a huge mesh molecule that
can surround the whole cell. You have specific pattern
recognition molecules that will recognize this. It's pretty much a
characteristic bacterial
cell wall compound for all types of bacteria. In particular, if you look at
the gram-negative bacteria, you can see that they have
their peptidoglycan wall as a single layer sandwiched
in between two membranes, the plasma membrane
and the outer one, and that they have a lot of lipopolysaccharides in
the outer membrane. That lipopolysaccharides
will also be a trigger to a different set of pattern recognition
molecules. The LPS is really a
very strong trigger of pattern recognition
reception that leads to an
inflammatory response. Here's a picture of one of
these lipopolysaccharides. You can see, here's

a lipid in the core. It's nailing this
into the membrane. Then we have some carbohydrates
sticking out from that. This is, again, a
different example of something that is very characteristic of
certain prokaryotes, and you have ways of identifying that and
responding to it. There are other molecules that
you can recognize as well, in particular, wrong
kinds of nucleic acids. If you have single-stranded
DNA, double-stranded RNA, DNA with the wrong kind
of methylation patterns, then you will react to it. Mice even have a specific
reaction where they can tell the 23S ribosomal component from their own small
ribosomal RNAs and have a specific
recognition for that. I don't think it's been
identified in humans yet. In addition to these pattern
recognition molecules, you have a number
of things that are extracellular that
you put out just to prevent yourself from kill
things before they get to you. We're back to, in this one, recognizing that
peptidoglycan wall again. What you have in mucus and
tears and other secretions at your body is something
called lysosine. This is synthesized
and secreted, and it specifically will
break up peptidoglycans. You have an enzyme to chew up bacteria before they
even get into you. There's something
called Psoriasin on the skin that you use
against the E. coli. It can be induced by sunlight. If you have too much of it,
you can actually get eczema. Too little of it, of course, the bacteria can get
you. There are also other
defensive peptides, and there are mannose
binding lactins in the plasma of the blood. We're going to look
at that when we look at complement activation. But there are again
specific kinds of carbohydrate
patterns and cells that involve several
mannoses one after the other that this
compound can recognize. Another really interesting
one is something called C reactive protein. C reactive protein
recognizes microbes, recognizes damaged cell cells in ways that we're not
entirely clear about. C reactive protein is a sign of general long
term inflammation, and you actually have to get tested for this in certain blood
tests and it's
associated with a heart attack if you
have an elevated level of this over a long period of time, whether
you're sick or not. There's also, again,
a particular protein that's designed just to bind to lipopolysaccharides
that's specifically there to recognize
gram-negative bacteria. In addition, in your cytoplasm, you have what are
called NOD proteins, which sometimes will
bind nucleic acid, sometimes will bind
cell wall compounds. But my favorite pattern
recognition cell is the toll like receptor. And here is a list of different
things that
they can recognize. Now, you can see there's nine of them on this
one. Excuse me. We found nine
identified in humans, another three more
that seem to be functioning either in mice or we're not entirely sure
what they're doing. This is an active
subject of research so this one may be a
little bit out of date. But on the whole, the toll like receptors recognize a
variety of compounds that are specific
to various pathogens. This one, these things are
eventually going to signal an inflammatory
response that will activate something
called NF -kB, which is a transcription
factor that will turn on a whole bunch of genes to help you fight various

infections. Let me just say you've got this. It's not that I wanted
you to memorize this, but I did want you to
realize there in a sense, going to be two
categories of this, some that are found in
the plasma membrane, and some that are found
in the endomembranes. Logically, the ones in
the plasma membrane are facing with their receptor
parts outwards so they can sample pathogens in the
environment and the ones in the endomembrane system are arranged with their
receptors facing inward. Here's a drawing of them. You can see here that you've
got a
receptor on the outside and a signaling region
on the cytoplasm side. In general, you have
things that recognize viral signatures,
particularly nucleic acids. Those are usually ones that are in the end
the membranes because they don't really work very well until you
chewed something up. On the other hand,
in the exterior, we have a whole bunch
of different ways of recognizing bacteria, eukaryotic threats, a variety
of bacteria, the flagellin. It's really interesting
because these things have a much lower specificity
than an antibody. That is, they recognize
categories of molecules, and if you put two
different ones together, mixing and matching
them will give you specificities that neither of the components has by itself,
and the specificities of one combination may differ
from using that same one. If I put two with one, I can recognize
bacterium parasites, but if I put two
together with six, I can recognize fungi in
addition to bacteria. Exactly what's going on
here is pretty interesting, but it's certainly not like
the enzyme substrate lock and key fit that we're going to see with antibody-
antigen
interactions. We've got regulation
for these things. We can turn them on,
we can turn them off. That is, if your inflammatory
response gets too strong, you can down regulate it. But these toll-like
receptors are among the most powerful
recognition molecules in the body for recognizing
pathogenic threats, and they also will trigger the recognition of a threat
in phagocytic organisms, and that's partly
what sends them off to present antigen to a TH cell. What we're going
to do after this then is take another look at how you will phagocytize and
then break up compounds. But again, a reminder
that you have also these toll-like
receptors poking into the endomembranes in order
to alert the cell when they find something
being phagocytized that represents a danger.